Public Health Partnership in Response to Resistant Gonorrhea: Role of Laboratories in Enhancing Local Capacity Towards Improved Gonococcal Surveillance

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INTRODUCTION

The Milwaukee Health Department Laboratory (MHDL) has been collaborating with local, state agencies and the Centers for Disease Control and Prevention (CDC) to monitor trends and develop strategies to combat the emergence of *Neisseria gonorrhoeae* (GC) antibiotic resistance (AR).

GC culture and antimicrobial susceptibility testing (AST) data is integrated into CDC's *Strengthening the United States Response to Resistant Gonorrhea* (SURRG) project involving 8 surveillance sites, to support a national public health response to resistant gonorrhea.

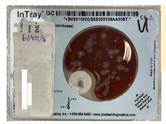
Isolates displaying clinically-relevant high minimal inhibitory concentrations (MICs) to Azithromycin (AZI), Cefixime (CFX) and Ceftriaxone (CRO) have emerged worldwide and have been on the rise within the last decade. GC nonsusceptible to AZI and CRO have each been isolated locally. The emergence of *N. gonorrhoeae* with decreasing susceptibilities to AZI and cephalosporins, together with the waning antimicrobial arsenal, present a major public health concern. Hence, enhanced surveillance systems like SURRG are needed to implement and strengthen STD prevention and control programs in partnership with state, local and territorial health departments.

Figure 1: New and continuing activities to combat drug resistant Gonorrhea at local and National level (1). County level data from CDC Atlas (2). The City of Milwaukee Health Department is both a GISP and SURRG site.

- **ARLN** (Antibiotic Resistance Laboratory Network)
- **GISP** (Gonococcal Isolate Surveillance Project)
- **SURRG** (Strengthening U.S. Response to Resistant Gonorrhea)
- **eGISP** (enhanced Gonococcal Isolate Surveillance Project)
- **SSuN** (STD Surveillance Network)

MATERIALS AND METHODS

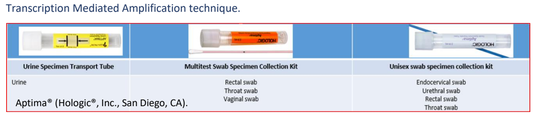
Collection and Transport: Specimens were collected from genital (endocervical, male urethral, vaginal) and non-genital sites (pharyngeal, rectal), per defined clinical criteria. At the STD clinic, specimens were collected on InTray GC™ and at non-STD clinics using eSwab™ and transported to MHDL within 24 hours.



InTray GC™ (BioMed Diagnostics, Inc., White City, OR)

eSwab™ (Copan Diagnostics, Inc., Murietta, CA)

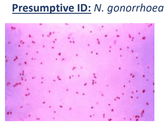
Screening (NAAT): Nucleic acid amplification testing (NAAT) specimens were collected and transported using Aptima® Collection & Transport Tubes. On the Hologic® Panther instrument GC nucleic acid detected within 4 hours using Transcription Mediated Amplification technique.



Urine Specimen Transport Tube	Multitest Swab Specimen Collection Kit	Unisex swab specimen collection kit
Urine	Rectal swab Throat swab Vaginal swab	Endocervical swab Urethral swab Rectal swab Throat swab

Aptima® (Hologic®, Inc., San Diego, CA).

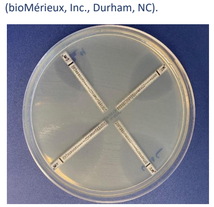
Presumptive ID: *N. gonorrhoeae* are Gram-negative diplococci that possess the enzyme cytochrome c oxidase.



Gram stain

Oxidase reaction

Susceptibility testing (Etest): Predefined gradient of antibiotic concentrations on a plastic strip used to determine the MIC of antibiotics: AZI, GEN, CFX, & CRO (bioMérieux, Inc., Durham, NC).

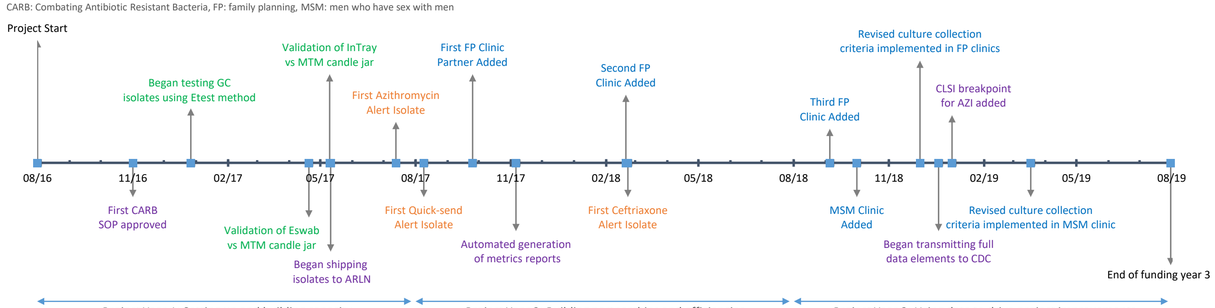


Confirmation (apiNH biochemical profile): More than 90% of GC produce acid from glucose (GLU) and proline aminopeptidase (ProA) (bioMérieux, Inc., Durham, NC).

*All isolates are also referred to Texas Department of State Health Services (TX-DSHS) for Agar Dilution and Whole Genome Sequencing

Timeline of SURRG milestones

CARB: Combating Antibiotic Resistant Bacteria, FP: family planning, MSM: men who have sex with men



RESULTS

GC culture results: GC was isolated in 19.3% of 5,445 samples tested. From April 2017 through April 2019, 896 out of 3530 (25.4%) patient specimens from the STD clinic and 157 out of 2161 (7.3%) from non-STD clinics tested culture positive. 3074 specimens were from males (26.3% positive), and 2364 from females (10.2% positive). 7 specimens did not identify patient sex (57.1% positive).

AST results: Of those, 1049 isolates had AST results, 56 (5.3%) were non-susceptible (NS) to AZI and two (0.2%) to CRO. CDC's MIC breakpoints were used for enhanced AR surveillance. Patients NS to any of three antibiotics were followed up by disease intervention specialists (DIS) to administer treatment, initiate partner therapy and recommend test of cure. AST results were available within 7 days of collection 97% of the time.

NAAT results: GC was detected in 6.73% of 27,346 samples. Majority of patients tested were males (81%). 67.3 % of GC positive cases were STD clinic patients.

All culture and AST data were shared monthly with WI Division of Health Services (WI-DHS), ARLN and CDC, and in real-time with all partners for 'Alert' and 'Quick-send Alert' isolates.

Figure 2: Number of specimens tested for GC—April 2017 through April 2019 at MHDL. Blue: STD clinic, Orange: Family Planning (FP) clinics, Green: MSM clinic. Darker shades indicate GC isolates. November 2018: Change in patient selection criteria at FP clinics. March 2019: Change in patient selection criteria at MSM clinic.

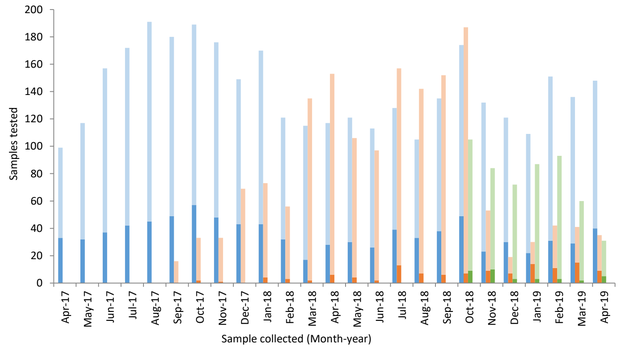


Figure 3: Percent positivity by specimen source and gender, April 2017-April 2019. A. Number of samples screened via NAAT, darker bars indicate RNA detected. B. Number of specimens cultured, darker bars indicate confirmed isolates.

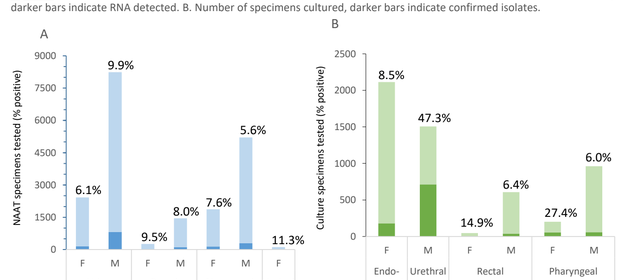


Figure 4: Number of Isolates with Elevated MICs (AZI ≥2.0 µg/ml, CRO ≥0.125 µg/ml), April 2017 – April 2019. Total Cases: 49. Female (18-29, median age = 22): 8, Male (16-58, median age: 28): 41, AZI MIC of 16: 4, AZI MIC of 8: 12, AZI MIC of 4: 7, AZI MIC of 2: 25. CRO MIC of 0.125: 2.

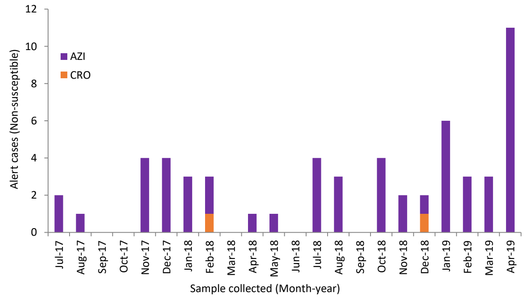
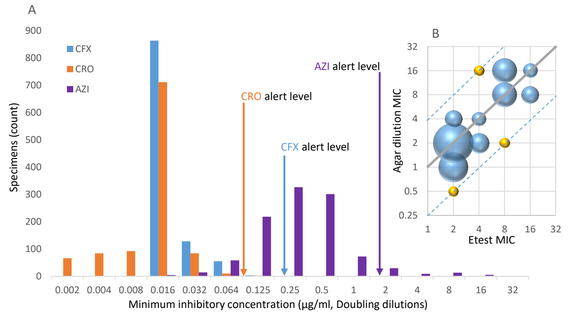
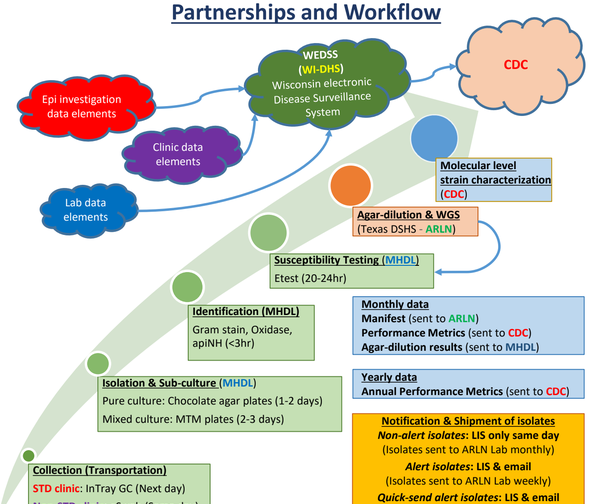


Figure 5: Etest results. A. Distribution of Etest MICs across all specimens collected April 2017-April 2019. Ceftriaxone range changed 11/2018 (0.016-256 → 0.002-32). B. Comparison of Etest and Agar Dilution results for all AZI Alert (nonsusceptible) specimens. Size of bubble indicates number of samples. No specimen exceeded CDC's reliability cut-off of ±2 doubling dilutions (orange circles, dotted lines).



Partnerships and Workflow



Quality Improvement Activities

- Patient selection criteria modified to include non-symptomatic patients with contact to STI, NAAT positive, TOC. Recovery rates improved from 80.9% of NAAT-positive specimens culture-positive in 2017 to 82.5% in 2018.
- Commercially available transport and collection kits with long expiration dates provided option for non-STD and STD clinics to send specimens to MHDL without the need for incubation, without loss of GC viability.
- Etest more accurate, sensitive, and reliable screening method help identify alert and quick send alert isolates. 49 Alert cases identified with Etest (2017-2019) compared to zero with disk-diffusion (2015-2017).
- Enhanced epidemiological investigation led to screening of 1st and 2nd generation partner cases.
- Enhanced surveillance helped identify intermediately resistant cases and confirm treatment success with TOC.
- Automated lab, clinic, and epi investigation data extraction led to timely and accurate information as of 11/2017.

CONCLUSIONS

- Jurisdictional awareness and capacity building for GC-AST at the local level in high risk populations will not only improve surveillance but will help rule out suspect treatment failure cases
- Real-time detection of GC resistance and strain typing in partnership with local, state, and CDC will further improve surveillance toward preventing local outbreaks
- Improve existing antibiotic treatment guidelines and provide evidence for altering treatment regimens

REFERENCES

1. Centers for Disease Control and Prevention, "Combating the Threat of Antibiotic-Resistant Gonorrhea." https://www.cdc.gov/std/gonorrhea/arg/carb.htm, accessed 5/28/2019
2. Centers for Disease Control and Prevention, "AtlasPlus." https://www.cdc.gov/nchhstp/atlas/, accessed 5/29/2019

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KEEP CALM AND SURRG ON
STRENGTHENING THE U.S. RESPONSE TO RESISTANT GONORRHEA
We can make a difference in Wisconsin and Nationally!

Think Health Act Now!
CITY OF MILWAUKEE HEALTH DEPARTMENT

Presented at the 2019 APHL Annual Meeting, St. Louis, MO.